UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/087,346	03/01/2002	Allen Comer	STRATA-06949	3073

7590 09/25/2003

MEDLEN & CARROLL, LLP
Suite 350
101 Howard Street
San Francisco, CA 94105

EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	8

DATE MAILED: 09/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/087,346	COMER ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE f this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election without traverse of group I, claims 1-6 and 8, in Paper No. 7 is acknowledged.

2. Claims 7 and 9-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7.

Claims 7 and 9-54 have been canceled. Claims 1-6 and 8 are pending and under consideration.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 6 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "NIKS" in claim 6 is vague and renders the claim indefinite. NIKS is an abbreviation that can have various different meanings. Spelling out the term as "near-diploid immortalized karatinocytes" would be remedial.

The phrase "derived from" in claim 8 is vague and renders the claim indefinite. It is unclear as to the metes and bounds of what would be considered "derived from". Keratinocytes "derived from" two different sources could mean that the keratinocytes are chemically modified

or generically modified, or unmodified at all. The specification fails to specifically define the phrase "derived from".

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 2, 5, 6 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a human skin equivalent having a surface electrical capacitance (SEC) of 40-240pf or 80-120pf after grafting in vivo as disclosed by Gorectsky et al., 1995, and Boyce et al., 1996, as discussed below, does not reasonably provide enablement for a composition comprising a human skin equivalent having a SEC of 40-240pf or 80-120pf in vitro, or a human skin equivalent comprising NIKS cells and SEC of about 40-240pf in vitro or in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1, 2, 5, 6 and 8 are directed to a composition comprising a human skin equivalent having a surface electrical capacitance (SEC) of from about 40-240 picofarads (pf) or 80-120pf, wherein the skin equivalent comprises primary karatinocytes or immortalized karatinocytes. Claim 6 specifies the immortalized keratinocytes are NIKS cells.

The specification grows NIKS cells on the dermal equivalents prepared within a 10mm MILLICELL insert with optimal media or sub-optimal media, and shows that higher total

ceramide content of the skin culture was obtained when the cells were grown in optimal media as compared to sub-optimal media. The claims encompass a composition comprising a human skin equivalent having a SEC of 40-240pf or 80-120pf, or a human skin equivalent comprising NIKS cells and SEC of about 40-240pf in vitro or in vivo.

The specification fails to provide adequate guidance and evidence how to prepare a human skin equivalent having a SEC of 40-240pf or 80-120pf in vitro. The specification also fails to provide adequate guidance and evidence whether growing NIKS cells on various substrate can result in human skin equivalent having SEC of about 40-240pf in vitro or in vivo. Boyce et al., 1996, (Journal of Investigative Dermatology, Vol. 107, No. 1, p. 82-87) discloses that SEC of a cultured skin substitutes (CSS) fluctuates in vitro and its SEC values are much higher than native murine or human skin. SEC of CSS in vitro shows time-dependent decrease from 4721 pf on day 3 to 394 pf on day 14 and subsequent increase to 1677 pf on day 21. After grafting, SEC of CSS decreases from 910 pf at 2 wk to 40 pf at 4 wk with no significant decrease thereafter (e.g. abstract, p. 83, right column). Goretsky et al., 1995, (Wound Repair and Regeneration, Vol. 3, No. 4, pp. 419-425) discloses that SEC of CSS before grafting in vivo is much higher than SEC of CSS after grafting and the SECs of the CSS on postoperative days 12, 14, 21 and 28 are 129, 200, 88 and 74 (+- deviations) pfs, which are comparable to the native skin. It appears that CSS or human skin equivalent in vitro has much higher SEC values and less barrier function as compared to native skins, i.e. CSS and human skin equivalent in vitro has SEC in the range of thousands of pf instead of 40-240 pf as observed in native skins. SEC of CSS or human skin equivalent decreases only after grafting in vivo where its structure is reconstituted. In view of the state of the art as discussed above and the lack of guidance and

evidence in the present application, one skilled in the art at the time of the invention would not know how to prepare a CSS or human skin equivalent having the claimed SEC values by using primary human keratinocytes or immnortalized keratinocytes, such as NIKS cells, in vitro. Thus, one skilled in the art would have to engaged in undue experimentation to practice over the full scope of the invention claimed.

This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 2 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Goretsky et al., 1995 (Wound Repair and Regeneration, Vol. 3, No. 4, pp. 419-425).

Claims 1, 2 and 5 are directed to a composition comprising a human skin equivalent having a surface electrical capacitance (SEC) of from about 40-240 or 80-120 picofarads (pf), wherein the skin equivalent comprises primary karatinocytes or immortalized karatinocytes.

Goretsky teaches preparation of cultured skin substitutes (CSS) by growing primary cultures of human epidermal keratinocytes and fibroblasts and inoculating these cells onto collagen-glycosaminoglycan biopolymer substrates. Goretsky records the SEC of the CSS on

postoperative days 12, 14, 21 and 28 at 129, 200, 88 and 74 (+- deviations) pfs. Thus, claims 1, 2 and 5 are anticipated by Goretsky.

9. Claims 1 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Boyce et al., 1996 (Journal of Investigative Dermatology, Vol. 107, No. 1, p. 82-87).

Claims 1 and 5 are directed to a composition comprising a human skin equivalent having a surface electrical capacitance (SEC) of from about 40-240 picofarads (pf), wherein the skin equivalent comprises primary karatinocytes or immortalized karatinocytes.

Boyce teaches preparation of CSS by culturing human epidermal fibroblasts and epidermal karatinocytes and shows SEC of the human skin substitute after grafting is about 40 pf. Thus, claims 1 and 5 are anticipated by Boyce.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boyce et al., 1996 (Journal of Investigative Dermatology, Vol. 107, No. 1, p. 82-87) in view of Suzuki et al., 1995 (Transplantation, Vol. 59, p. 1236-1241).

Claims 1 and 8 are directed to a composition comprising a human skin equivalent having a surface electrical capacitance (SEC) of from about 40-240 picofarads (pf), wherein the skin equivalent comprises karatinocytes derived from two different sources.

Boyce teaches preparation of CSS by culturing human epidermal fibroblasts and epidermal karatinocytes and shows SEC of the human skin substitute after grafting is about 40 pf.

Boyce does not specifically teach using mixture of keratinocytes for generating skin substitute.

Suzuki teaches culturing mixture of syngeneic and allogeneic mouse keratinocytes and the resulting sheets of keratinocytes were implanted subcutaneously into adult mice. Suzuki suggests that "graftable skin substitutes may be produced by co-culturing a small amount of autologous keratinocytes with allogeneic keratinocytes, which are readily available " (e.g. abstract).

It would have been obvious for one of ordinary skill in the art at the time of the invention to substitute the keratinocytes as taught by Boyce with the mixed culture of syngeneic and allogeneic mouse keratinocytes as taught by Suzuki because Suzuki teaches using mixed culture of keratinocytes to generate skin substitute. It also would have been obvious for one of ordinary

skill in the art to use mixed culture of human keratinocytes to generate skin substitute because both Boyce and Suzuki teach using keratinocyte to make skin substitute and the teaching of Suzuki of using mixed culture of keratinocytes would make it obvious for one of ordinary skill to use mixture of human keratinocytes for preparing skin substitutes.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to generate skin substitute for the treatment of acute and chronic skin wounds as taught by Boyce and Suzuki with reasonable expectation of success.

13. Claims 1, 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boyce et al., 1996 (Journal of Investigative Dermatology, Vol. 107, No. 1, p. 82-87) in view of Ponec et al., 1997 (Journal of Investigative Dermatology, Vol. 109, No. 3, p. 348-355).

Claims 1, 3 and 4 are directed to a composition comprising a human skin equivalent having a surface electrical capacitance (SEC) of from about 40-240 picofarads (pf), wherein the combined content of ceramide 5, 6 and 7 in said skin equivalent is about 20-50% or 10-40% of the total ceramide content.

Boyce teaches preparation of CSS by culturing human epidermal fibroblasts and epidermal karatinocytes and shows SEC of the human skin substitute after grafting is about 40 pf.

Boyce does not specifically teach the combined content of ceramide 5, 6 and 7 in the skin equivalent is about 20-50% or 10-40% of the total ceramide content.

Ponec teaches that ceramide contents of ceramide 4-7 in various human skin equivalents are lower than those of native tissues, especially ceramides 6 and 7 are much lower that those of

native tissues. Ponec teaches culturing the human skin equivalent in medium containing Vitamin C markedly increased contents of ceramides 6 and 7, and the combined content of ceramides 5-7 is about 23% to 35% of total ceramide content while growing the human keratinocytes on different substrates (e.g. abstract, Table III).

It would have been obvious for one of ordinary skill in the art at the time of the invention to prepare a human skin equivalent having combined content of ceramides 5-7 of about 23% to 35% of total ceramide content in vitro as taught by Ponec and grafting the skin equivalent in vivo to obtain comparable SEC values as compared to native tissue as taught by Boyce because both Boyce and Ponec teach preparation of human skin equivalent that is comparable to human native skin and lower SEC values and higher ceramide 4-7 content are index of barrier function of the human skin equivalent.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to generate human skin substitute having barrier function that is comparable to the native human skin, i.e. having lower SEC values and higher ceramide 4-7 content, with reasonable expectation of success.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.